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Does Photodynamic Therapy Improve The Survival Rate Of Patients With Unresectable Cholangiocarcinoma?

Tyler C. Hafer
Philadelphia College of Osteopathic Medicine

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Tyler C. Hafer, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not photodynamic therapy improves the survival rate of patients with unresectable cholangiocarcinoma.

Study Design: Systematic review of two randomized controlled trials and one retrospective cohort study published in 2014, 2014, and 2016.

Data Sources: Two randomized controlled trials and one retrospective cohort study examining photodynamic therapy in patients with unresectable cholangiocarcinoma. Data sources were found using PubMed and EBSCOhost.

Outcome(s) Measured: Overall survival and progression free survival were measured in patients who underwent photodynamic therapy for unresectable cholangiocarcinoma. Each study analyzed overall survival using a Kaplan-Meier survival curve.

Results: The RCT by Hauge et al. found photodynamic therapy to improve overall survival rate in patients with unresectable cholangiocarcinoma compared to patients who did not receive photodynamic therapy. The RCT by Park et al. found photodynamic therapy plus oral flouropyrimidine to improve overall survival over photodynamic therapy alone. The retrospective cohort study by Strand et al. was found to show no significant difference in overall survival with patients who underwent ERCP-directed radiofrequency ablation versus ERCP-directed photodynamic therapy.

Conclusions: There is conflicting evidence as to whether photodynamic therapy improves the survival rate of patients with unresectable cholangiocarcinoma. Further

Key Words: Photodynamic therapy, cholangiocarcinoma, overall survival

INTRODUCTION

Cholangiocarcinoma is a rare and debilitating cancer of the biliary tract. The majority of cholangiocarcinoma cases are not detected until metastasis has occurred and there is no chance of cure through medical intervention. The prognosis of a patient with cholangiocarcinoma is not good even with early detection and traditional treatment that includes chemotherapy and radiation. This systematic review evaluates two randomized controlled trials (RCT) and one retrospective cohort study comparing the efficacy of photodynamic therapy with traditional treatment methods for unresectable cholangiocarcinoma to traditional treatment methods such as chemotherapy and radiation.

Cholangiocarcinoma is a rare cancer that is increasing in incidence every year. This aggressive malignancy has about 5,000 newly diagnosed cases each year.[1] The incidence of cholangiocarcinoma is very high in Southeast Asia, but the number of cases are steadily increasing in the United States. A patient diagnosed with cholangiocarcinoma warrants the highest oncologic care available. High-level care comes with a high-level price in hospital equipment, utilities, staff, and medicine. The number of hospital admissions for patients with cholangiocarcinoma was 11,970.[2] The average length of stay of hospital admissions in 2012 was 7.9 days.[2] The majority, if not all, of the patient hospital admissions require nurses, physicians, unit clerks, hospital rooms, equipment, utilities, and medications which can make each stay exceptionally expensive. In 2012, the average cost for a cholangiocarcinoma patient's hospital charges was $77,753.[2]

The most common location for cholangiocarcinoma is the perihilar region of the biliary tract.[1] The perihilar area of the biliary tract is the junction where the left hepatic

duct and the right hepatic duct join together to form the common bile duct. Tumors in the perihilar location of the biliary tract are known as Klatskin tumors.[3] Most patients who suffer from cholangiocarcinoma are over the age of 60 and more commonly males.[2] Patients look to seek medial treatment typically for abdominal pain and/or jaundice of skin and sclera of the eyes.[2] Cholangiocarcinoma coincides with a multitude of complications that severely inhibit the quality of life of a patient. These complications include, but are not limited to, cachexia, cholestasis, cholangitis, biliary obstruction, and hepatic dysfunction.[1] Evaluation of the patient typically involves imaging studies that show biliary mass on abdominal ultrasound followed by MRI or magnetic resonance cholangiopancreatography (MRCP) and biopsy to diagnose if not confirmed on imaging.[2]

The gold standard of treatment for cholangiocarcinoma is surgical resection of the disease.[1] However, surgical resection is often not possible because the disease is often detected too late for a patient to be a candidate for surgical resection due to metastasis or risks outweighing the benefits of the surgery concerning the quality of life of the patient. Other standard forms of treatment include biliary stents to alleviate obstruction of the biliary tract. These stents include temporary plastic stents and self-expandable metal stents.[1] The stents are placed in the biliary tract via endoscopy or interventional radiology which is minimally invasive to the patient.[1] Typical standards of care for cholangiocarcinoma include chemotherapy and radiation.[1] Other adjuvant therapies include transarterial chemoembolization, percutaneous transhepatic cholangiography tubes, transarterial embolization, and liver transplantation.

The five-year survival rate of patients with cholangiocarcinoma is approximately 15%.[3] Photodynamic therapy is an ablation therapy that uses localized photosensitization

to make the targeted cells become necrotic or induce apoptosis.[1] Research has shown mixed results of photodynamic therapy improving survival rate of patients with unresectable cholangiocarcinoma as isolated therapy. Research shows that endoscopic retrograde cholangiopancreatography (ERCP) with photodynamic therapy is associated with improved survival rate compared to only biliary stent placement.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not photodynamic therapy improves the survival rate of patients with unresectable cholangiocarcinoma.

METHODS

Studies for this EBM were selected based on the population, intervention, comparison, outcome, and type of study in each article. This EBM selected two randomized controlled trials (RCT) and one retrospective cohort study that evaluated patients between the ages of 35-79 with unresectable cholangiocarcinoma for median progression free survival rate and one year survival rate. Interventions in the studies included photodynamic therapy, ERCP directed photodynamic therapy, and photodynamic therapy plus biliary stent plus Gemcitabine and Capacitabine (GemCap). Comparison groups included Photodynamic therapy plus oral flouropyrimidine, ERCP directed radiofrequency ablation, and biliary stent plus GemCap.

Data sources were articles found using searches through PubMed and EBSCOhost with keywords including “cholangiocarcinoma”, “photodynamic therapy”, and “randomized controlled trial”. All articles selected were published in the English language. Each article was published in a peer-reviewed journal. The author of this

systematic review performed all of the research used in this paper. The articles were selected based on their relevance to the clinical question, "Does photodynamic therapy improve the survival rate of patients with unresectable cholangiocarcinoma?" The inclusion criteria for this review was randomized controlled trial or retrospective cohort study published after 2012 with patients with unresectable cholangiocarcinoma. This review excluded patients who were under the age of 18 and patients who had resectable cholangiocarcinoma. In order to determine the significance of the results published in the articles, the numbers needed to treat (NNT), absolute benefit increase (ABI), relative benefit increase (RBI), and p-values were calculated. One article had continuous data that could not be statistically converted but was quantified I median number of days of survival.[3] One article had a p-value that was recorded, however, this article had continuous data that could not be statistically converted and was calculated as median number of months survived.[1] One article had dichotomous data that listed a p-value.[4] This article had data that was able to have calculations of numbers needed to treat, absolute benefit increase, and relative benefit increase.

Table 1 – Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Hauge[3], 2016	RCT	20	35-75	Unresectable or recurrent/ metastatic biliary tract cancer with no previous chemo or radiation therapy, no	Evidence of ongoing infection and life expect-ancy of < 3 months	5	Stent, temoporfin/ photodynamic therapy, GemCap

				additional cancer within last 5 years			
Park[4], 2014	RCT	51	64 ± 11	Patients with locally advanced unresectable hilar cholangio-carcinoma with no prior chemotherapy or radiotherapy, no serious or uncontrolled medical illness, adequate bone marrow function	Porphyria or previous placement of biliary metal stent	8	Photodynamic therapy
Strand[1], 2014	Retrospective Cohort Study	48	55-79	Patients over 18 years old diagnosed with unresectable cholangio-carcinoma	Patients who were capable of having surgical resection of cholangio-carcinoma	0	ERCP directed photodynamic therapy

OUTCOMES MEASURED

The outcomes measured in all three studies were patient overall survival after treatment with photodynamic therapy. Studies measured survival time from the day the patient entered into the trial until the day of the patient's death.[1,3,4]

In the article by Strand et al., the primary outcome measured was the overall survival of patients in months. Total months were calculated starting from the time the

patient received the intervention until patient death. Median survival of patients in the intervention and comparison groups was analyzed using a Kaplan-Meier survival curve.[1]

In the article by Hauge et al., the outcomes measured were progression free survival and overall survival. Both outcomes were calculated into median number of days for both the intervention group and the comparison group. Ten patients were in each group respectively. The data used to determine outcome measurements was started on the day of initial randomization of the study until the day of patient death. Median overall survival was analyzed using a Kaplan-Meier survival curve.[3]

In the article by Park et al., overall survival and progression free survival were measured. The time of data calculation was from the date of randomization until the date of patient death for overall survival. Progression free survival was measured from date of randomization until date of death or disease progression. Overall survival and progression free survival were analyzed using two separate Kaplan-Meier curves.[4]

RESULTS

This systematic review used two RCTs and one retrospective cohort study that displayed both continuous and dichotomous data comparing photodynamic therapy versus other treatment methods for unresectable cholangiocarcinoma that will be discussed later in this review. Each study had inclusion and exclusion criteria for the selection of patients, which can be found in Table 1.

In the retrospective cohort study by Strand et al., 48 patients with unresectable cholangiocarcinoma agreed and gave consent to be included in this study that received ERCP treatment between January 2008 and September 2012 at a tertiary-care academic medical center.[1] The patients were divided into two groups based on the type of treatment

the patient received. The first group consisted of 16 patients who received ERCP-directed radiofrequency ablation.[1] The second group consisted of 32 patients who received ERCP-directed photodynamic therapy.[1] At the time of statistical analysis, 4 out of 16 patients (25%) were alive in the radiofrequency ablation group.[1] The median survival of this group was 9.6 months with a confidence interval of 95%.[1] The range of survival in the group was 5.1-11.7 months.[1] At the same time, 0 out of 32 patients (0%) were alive in the photodynamic therapy group.[1] The median survival of the group was 7.5 months with a confidence interval of 95%.[1] The range of survival in the group was 4.3-16 months.[1] A Kaplan-Meier survival curve analyzed the survival rate of patients who received ERCP-directed radiofrequency ablation and ERCP-directed photodynamic therapy. The difference in overall survival between patients of either group was not statistically significant with a p-value of 0.799 (see table 2).[1] Strand et al also calculated an adjusted survival rate for both groups based on factors of age, sex, distant metastasis, time between diagnosis and initial treatment, and radiofrequency ablation using the Cox proportional hazard model.[1] The only variable of that showed a statistically significant negative correlation with survival was distant metastasis with a p-value of 0.014.[1]

Table 2: Overall survival rate of ERCP-directed therapy[1]

Group	Overall survival rate	P-value
ERCP-directed radiofrequency ablation therapy	9.6 months	0.799
ERCP-directed photodynamic therapy	7.5 months	0.799

In the RCT by Hauge et al., 20 patients with unresectable cholangiocarcinoma agreed and gave consent to participate in the study that took place from June 2008-

November 2011.[3] The 20 patients were randomized into two groups, Arm A and Arm B. Arm A consisted of 10 patients who were to receive photodynamic therapy plus a biliary stent plus GemCap (Gemcitabine 1000 mg/m^2 day 1 and day 8 and Capacitabine 650 mg/m^2 two times a day days 1-14 every third week).[3] During the study 3 patients in Arm A were unable to receive GemCap due to progression of infection and only received photodynamic therapy plus a biliary stent.[3] Arm B consisted of 10 patients who were to receive GemCap plus a biliary stent.[3] During the study two patients withdrew from the study and only received a biliary stent due to thrombocytopenia.[3] Hauge et al. found that Arm A had a median survival rate of 311 days for 7 patients who received photodynamic therapy plus stent plus GemCap.[3] The range of survival was 178-1060 days.[3] Arm B had a median survival rate of 336 days for 8 patients who received GemCap plus stent.[3] The range of survival was 110-690 days.[3] Median progression free survival of the 7 Arm A patients was 175 days with a range of 90-600 days.[3] Arm B had a median progression free survival of 96 days with a range of 56-422 days (see table 3).[3] Hauge et al. created a Kaplan-Meier survival curve to analyze the difference of median overall survival between the two groups. There was no adverse effects to the therapy reported by Hauge et al.[3] Only 15 patients that were included in the study at time of data collection completed the intended therapy without withdrawal or alteration in treatment.[3] Statistical values were in published in this RCT.

Table 3: Median overall survival in days[3]

Group	Median Overall Survival
Arm A (Photodynamic therapy+GemCap+Stent)	311 days
Arm B (GemCap+Stent)	336 days

In the RCT by Park et al., 43 patients with unresectable cholangiocarcinoma agreed and gave consent to participate in the study that took place from February 2009 to May 2012.[4] The 43 patients were randomized into two groups. The first group, Group A, had 21 patients and was given photodynamic therapy plus oral flouropyrimidine.[4] The second group, Group B, had 22 patients was given only photodynamic therapy.[4] Park et al. found that Group A patients had a one year survival rate of 76.2% compared to 32% Group B patients who were given only photodynamic therapy.[4] A log-rank test was used to evaluate the results which were found to be statistically significant with a p-value of 0.003.[4] The median overall survival of patients in group A was 17 months with a confidence interval of 95%.[4] Group B median overall survival was 8 months with a confidence interval of 95%.[4] This data was then analyzed on a Kaplan-Meier curve. A log-rank test was used to evaluate the results which were found to be statistically significant with a p-value of 0.005.[4] Relative benefit increase (RBI) was calculated to be -58% and absolute benefit increase (ABI) was calculated to be -44.2%. Numbers needed to treat (NNT) was calculated to be -2, (see table 4) meaning that for every 2 patients treated with photodynamic therapy, one less patient will survive one year after the time treatment is started compared to control. There were no adverse effects in Group B. In group A, 7 patients presented with toxicity (6 non-hematologic, 1 hematologic).[4] Adverse events related to tumor progression in patients such as metastasis. At the conclusion of the follow-up period of the study, 3 patients from Group A were alive and 1 patient from Group B.[4] The overall survival rate of patients treated with photodynamic therapy was significantly less than patients treated with photodynamic therapy plus oral flouropyrimidine for unresectable cholangiocarcinoma.[4]

Table 4: Analysis of treatment efficacy and statistical significance[4]

Study	CER	EER	RBI	ABI	NNT	P-value
Park	76.2%	32%	-58%	-44.2%	-2	0.003

DISCUSSION

Photodynamic therapy's mechanism of action requires a photosensitizing agent, such as temoporfin, that enters the patient intravenously.[5] The photosensitizing agent is then exposed to a light source calibrated to a specific wavelength of intensity depending on the location of the target tissue.[5] This light then creates oxygen with the photosensitizing agent to create cellular apoptosis that ultimately leads to cell death.[5] Cancer cells are more susceptible to the oxygen that is generated than normal cells. Normal cells do not retain the photosensitizer as long as cancer cells which is why the light therapy is administered 1-3 days after the patient is given the photosensitizer.[5] The light source of the therapy typically comes from a laser. Adverse effects of photodynamic therapy include photosensitivity for up to six weeks after treatment, scarring, burns, and pain to affected tissue.[5] Photodynamic therapy is considered a localized therapy that is contraindicated in cancers that have metastasized and cancers that may have too much growth or large surface area.[5] The main limitation of therapy is that the target site must be close to the skin to be efficient due to the penetrating ability of light through the skin.

The FDA does not currently approve photodynamic therapy for treatment of cholangiocarcinoma as clinical trials are still evaluating the effectiveness of the therapy.[5] The studies that were analyzed in this systematic review had limitations of small sample sizes and different comparison groups to the intervention. Small sample sizes could be

attributed to the small number of cases of unresectable cholangiocarcinoma. Other limitations included complications from the cancer such as cholangitis, infection, and biliary tract obstruction.[1,3,4]

CONCLUSION

There is conflicting evidence as to whether photodynamic therapy improves the survival rate of patients with unresectable cholangiocarcinoma. The study by Strand et al. reported no statistical significance between survival rates between ERCP-directed radiofrequency ablation and ERCP-directed photodynamic therapy. The RCT by Hauge et al. reported progression free survival rate to be greater in patients who received photodynamic therapy. The RCT by Park et al. showed that patients who received photodynamic therapy plus oral flouropyrimidine had better overall survival than patients with photodynamic therapy.

Increased study size is suggested for future studies. None of the studies in this review exceeded 50 patients that consented to participate. Patients in the studies analyzed had various complications from cholangiocarcinoma that skewed the results of the study and may have contributed to hasten death in patients that are very difficult to control in future studies.

Future consideration in the research of photodynamic therapy in unresectable cholangiocarcinoma is to increase the size of participants. Further investigation is warranted in the combination of combination therapy of photodynamic therapy with different chemotherapy and radiation. Future study to evaluate photodynamic therapy and photodynamic therapy plus adjuvant therapy for unresectable cholangiocarcinoma is required to substantiate the results in this review.

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